set forth in SEQ. ID. NO. 14. Nucleic acid encoding this enzyme includes molecules with the sequence of nucleotides set forth in SEQ. ID. NO. 13.

Please replace the paragraph on page 29, line 6 through page 31, line 20 with the following:

Resistant or altered enzymes, or nucleic acids encoding resistant or altered enzymes, as referred to throughout all of the many methods provided herein, may include any one or more of the above-referenced enzymes and nucleic acids as well as any of the following:

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 32;

nucleic acid containing the sequence of nucleotides 67 to 1611 in SEQ. ID. NO. 31;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 30 except that the codon for amino acid 333 encodes an amino acid other than threonine;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 30 except that the codon for amino acid 351 encodes an amino acid other than serine;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 30 except that the codon for amino acid 333 encodes an amino acid other than threonine and the codon for amino acid 351 encodes an amino acid other than serine;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 2 except that the codon for amino acid 333 encodes an amino acid other than threonine;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 2 except that the codon for amino acid 351 encodes an amino acid other than serine;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 2 except that the codon for amino acid 333 encodes an amino acid other than

threonine and the codon for amino acid 351 encodes an amino acid other than serine;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 4 (or as set forth in SEQ. ID. NO. 4 except that amino acids 190 and 191 are alanine and glycine, respectively);

nucleic acid containing the sequence of nucleotides 48 to 1589 in SEQ. ID. NO. 3 (or the sequence of nucleotides 48 to 1589 of SEQ. ID. NO. 3 except that the sequence of nucleotides 614-619 is TGCAGG instead of CCGCAG);

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 2, except that the codon for amino acid 277 encodes an amino acid other than glutamine;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 2, except that the codon for amino acid 462 encodes an amino acid other than alanine;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 2, except that the codon for amino acid 277 encodes an amino acid other than glutamine and the codon for amino acid 462 encodes an amino acid other than alanine;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 2, except that the codon for amino acid 456 encodes an amino acid other than phenylalanine and the codon for amino acid 470 encodes an amino acid other than aspartic acid;

nucleic acid encoding the amino acid sequence set forth in any of SEQ. ID. NO. 6, SEQ. ID. NO. 8, SEQ. ID. NO. 10 and SEQ. ID. NO. 12;

nucleic acid containing the sequence of nucleotides 48 to 1589 in any of SEQ. ID. NO. 5, SEQ. ID. NO. 7, SEQ. ID. NO. 9 and SEQ. ID. NO. 11;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 24;

nucleic acid containing the sequence of nucleotides 4 to 1101 in SEQ. ID. NO. 23;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 22 except that the codon for amino acid 26 encodes an animo acid other than histidine;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 20 except that the codon for amino acid 56 encodes an animo acid other than histidine;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 22 except that the codon for amino acid 105 encodes an amino acid other than valine;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 22 except that the codon for amino acid 105 encodes a glutamic acid residue;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 20 except that the codon for amino acid 134 encodes an amino acid other than valine;

nucleic acid encoding the amino acid sequence set forth in SEQ. ID. NO. 20 except that the codon for amino acid 134 encodes a glutamic acid residue.

Please replace the paragraph on page 46, line 14 through page 47, line21 with the following:

As used herein, "at a position corresponding to" refers to a position of interest (*i.e.*, base number or residue number) in a nucleic acid molecule or protein relative to the position in another reference nucleic acid molecule or protein. Corresponding positions can be determined by comparing and aligning sequences to maximize the number of matching nucleotides or residues, for example, such that identity between the sequences is greater than 95%, greater than 96%, greater than 97%, greater than 98% or greater than 99%. The position of interest is then given the number assigned in the reference nucleic acid molecule. For example, it is shown herein that a particular alteration in human inosine monophosphate dehydrogenase (IMPDH) occurs at amino acid residue position 333 of SEQ. ID. No. 2. To identify the corresponding amino acid in another isolate, the sequences are aligned and then the position that lines up with 333 is identified. The same process may be applied to identify a nucleotide in a nucleotide sequence that corresponds to a particular nucleotide position in another nucleotide sequence.

Since various alleles or isolates may be of different length, the position designated, for example, amino acid 333 may not be amino acid 333, but instead is at a position that "corresponds" to the position in the reference sequence.

Please replace the paragraph on page 72, line 27 through line 32 with the following:

Selection systems based on a resistant IMPDH as a selectable marker may be used in several formats in connection with the transfer of nucleic acids into cells that predominantly express IMPDH type I. In one format, the cells may be transfected with DNA encoding an IMPDH type I enzyme that is resistant to an inhibitor of IMPDH type I and then cultured in the presence of the inhibitor.

Please replace the paragraph on page 80, line 28 through page 81, line 6 with the following:

Inhibitors of DHODH may also be identified in a variety of screening assays. For example, candidate inhibitory compounds may be tested for ability to inhibit DHODH activity assessed in spectrophotometric assay. Two such assays are coupled assays, based on the ability of active enzyme to transfer electrons through ubiquinone to an acceptor (NBT or DCIP) in the presence of dihydroorotate. Thus, DHODH activity may be determined by monitoring the reduction of NBT or DCIP as a change in absorbance at 610 nm of a reaction mixture containing ubiquinone, dihydroorotate, DHODH and either NBT or DCIP (see, *e.g.*, Davis *et al.* (1997) *Biochem. Pharmacol. 54(4)*:459-465).

Please replace the paragraph on page 85, line 6 through line 16 with the following:

The activity and inhibitor sensitivity of inhibitor-resistant or altered DHODH enzymes may be evaluated using assays as described herein or any assay known in the art for measuring DHODH activity. Two such methods involve colorimetric assays, the nitroblue tetrazolium (NBT) assay and 2,6-dichloroindophenol (DCIP) assay (see, e.g., Davis *et al.* (1997) *Biochem. Pharmacol. 54(4)*:459-465, and Knecht *et al.* (2000) *Chemico-Biological Interactions 124*:61-76). Both assays are coupled assays, based on the ability of active enzyme to transfer electrons through

ubiquinone to an acceptor (NBT or DCIP) in the presence of dihydroorotate. The reduction of these compounds produces a change in their absorption spectra which can be monitored spectrophotometrically.

Please replace the paragraph on page 101, line 30 through page 102, line 21 with the following:

Stimulation and activation of lymphocyte host cells in connection with the transfer of nucleic acids encoding a resistant IMPDH and/or DHODH into the cells may be performed prior to, during and/or after delivery of the nucleic acids to host cells using methods known to those skilled in the art. Such methods may include, but are not limited to, contacting host cells with antigens, monoclonal antibodies, cytokines, growth factors, mitogens and combinations thereof. For example, in an exemplary protocol, human peripheral blood mononuclear cells (PBMC) or mouse splenocytes which have been stimulated *in vitro* with anti-CD3 mAb and IL-2 are cultured for 19.5 to 20 hours in medium containing PHA or Con A, respectively, prior to electroporation-facilitated delivery of heterologous nucleic acids to the cells (see, *e.g.*, Hughes *et al.* (1996) *J. Biol. Chem. 271*:5369-5377 and Cron *et al.* (1997) *J. Immunol. Meth. 205*:145-150). In another protocol, mouse B cell blasts are stimulated with LPS (*E. coli* 055:B5; Sigma Chemcial Co., St. Louis, Missouri) for 24 hours and then cocultured (4 x 10^6 cells/ml; 6-ml cultures) with virus-producer monolayers in the presence of 50 μg/ml LPS for 24 hours for retroviral-mediated delivery of heterologous nucleic acids to the cells (see, *e.g.*, Agarwal *et al.* (2000) *J. Clin. Invest.106:*245-252 and Zambidis *et al.* (1997) *Mol. Med. 3:*212-224). In a further protocol, lymphocytes are transfected after culture for three days with IL-2 and PHA (see, *e.g.*, Cann *et al.* (1988) *Oncogene 3*:123] or Con A [see, *e.g.*, Novak *et al.* (1992) *Mol. Cell. Biol. 12*:1515).

Please replace the paragraph on page 111, line 26 through page 112, line 15 with the following:

Selection systems provided herein which are specific for the selection of cells containing selectable markers as described herein are particularly useful in connection with treatment of immune disorders, such as primary (congenital)

immune deficiency, secondary (acquired) immune disorders and autoimmune disorders, that involve transfer of nucleic acids to lymphocytes, bone marrow cells, or other cells beneficial for the treatment of immune disorders. Primary immune deficiency disorders include, but are not limited to, antibody deficiencies, combined immunodeficiencies, complement deficiencies, and phagocytic cell deficiencies including, but not limited to, X-linked Agammaglobulinemia, severe combined immunodeficiency (SCID), adenosine deaminase (ADA) deficiency, C2 deficiency, purine nucleoside phosphorylase deficiency, granulomatous disease, and leukocyte adhesion deficiency. Secondary immune disorders include, but are not limited to, AIDS, and those resulting from malnutrition, neoplasia and infections. Autoimmune disorders include, but are not limited to, Type I diabetes mellitus, inflammatory bowel disease (*e.g.*, Crohn's disease and ulcerative colitis), systemic lupus erythematosus, chronic active hepatitis, multiple sclerosis, Grave's disease, Hashimoto's thyroiditis, Behcet's syndrome, myasthenia gravis, Sjogren's syndrome, pernicious anemia, idiopathic adrenal insufficiency and polyglandular autoimmune syndromes Type I and II.

Please replace the paragraph on page 118, line 4 through line 14 with the following:

Bone marrow transplantation (BMT) is most often associated with graft-versus-host disease (GVHD) in which the alloreactive T cells within the transplanted healthy bone marrow attack the recipient's (host's) cells as though they were foreign organisms. One treatment for graft-versus-host disease involves immunosuppressants such as *de novo* purine and pyrimidine biosynthesis inhibitors. Because bone marrow is unable to adequately salvage nucleotides (see, e.g., Xu *et al.*, (1998) *J. of Immun. 160*:846-853), treatment with such compounds results in myelotoxicity and possible loss of bone marrow graft. Immunosuppression also results in depletion of anti-tumor T-cells inhibiting the patient's natural defense against malignancies.

Please r place the paragraph on page 119, line 23 through page 120, line 10 with the following:

The selection systems provided herein are particularly suitable for use in selection of genetically modified hematopoietic stem cells. The ability of hematopoietic stem cells to undergo substantial self-renewal as well as the ability to proliferate and differentiate into all of the hematopoietic lineages makes hematopoietic stem cells the target of choice for a number of gene therapy applications. In a particular embodiment of the systems provided herein, hematopoietic stem cells may be engineered to produce an inhibitor-resistant IMPDH and/or DHODH enzyme which serves as a selectable marker therein. Engineered cells containing a selectable marker may also contain other therapeutic genes for treatment of diseases amenable to gene transfer into hematopoietic stem cells. Such diseases may include, but are not limited to, viral infections, malignancies, thalassaemia, sickle cell anemia, adenosine deaminase deficiency, recombinase deficiency, recombinase regulatory gene deficiency, Hunter syndrome, Hurler syndrome, and Gaucher's disease. Diseases other than those associated with hematopoietic cells can also be treated by genetic modification of hematopoietic stem cells. Such diseases may be related to the lack of a particular secreted product including, but not limited to, hormones, enzymes, interferons, and growth factors.

Please replace the paragraph on page 145, line 6 through line 21 with the following:

The 1.545 kb altered IMPDH II fragment was subcloned into the multiple cloning site in the second transcriptional unit of the expression vector pMG (InvivoGen, San Diego, California; see SEQ ID NO. 33 for the nucleotide sequence of pMG). Insertion of the altered IMPDH II cDNA into this multiple cloning site of pMG places the cDNA under the control of a modified human Elongation Factor-1α/Human T cell Leukemia virus hybrid (EF-1α/HTLV) which provides high expression levels in all cell types independent of cell cycle. The promoter is modified to enhance stability of DNA and RNA using the R segment and part of the